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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,967	04/07/2000	MATS WAHLGREN	45300-59676	4801

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YOUNG & THOMPSON
745 SOUTH 23RD STREET 2ND FLOOR
ARLINGTON, VA 22202

EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,967	WAHLGREN ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 2 sheets
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed December 12, 2003 is acknowledged and has been entered. Claims 1-38 have been canceled. New claims 39-51 have been added and are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite because they contain the abbreviations "DBL-1". Full terminology should be in each instance in the claims without the additional use of redundant abbreviations in parentheses or otherwise. Correction is required. Claims 41, 47 and 51 are vague and indefinite in the recitation of a molecular weight; how is the molecular weight determined? The claims should recite how the molecular weight was determined. Claim 44 is vague and indefinite in the recitation of "DB:-1"; what does Applicant intend?

4. The rejection of claims 43-45, 48 and 50 under 35 U.S.C. § 112, first paragraph, because the specification is not enabled for the scope of enablement for a pharmaceutical, vaccine or medicament comprising the polypeptide or any

amino-terminal part of the polypeptide of SEQ ID NO: 1 is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 24, 33, 34 and 38 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed April 1, 2003, have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that they "...believe that due to constant human immune pressure, PfEMP1 molecules are variable in size and sequence. However, an increasing pool of data indicates that only a few species of PfEMP1 can cause severe episodes like cerebral or placental malaria. Interestingly, these PfEMP1s seem to be commonly recognized by antibodies from individuals who are resistant to severe malaria. Thus, it's likely that cerebral malaria or placental malaria can be prevented through immunizations with one or a few species of PfEMP1." (Amendment, pp.10-11). It is noted that Applicants have not provided any evidence of this belief.

Applicants refer to Carlson et al, 1999 and Chen et al, 2003 to indicate that the DBL-1 domain is the most conserved domain of the PfEMP1 domain. However, these references have not been provided. No citation has been provided.

Applicants have asserted that they have discovered that immune-antibodies generated by a vaccination with recombinant PfEMP1-DBL-1 constructs of FCR3S1.2 recognize native PfEMP1 on a live infected red blood cell surface, disrupt preformed *P. falciparum* rosettes and hinder the adhesion of infected erythrocytes in an animal model, (newly developed rat model, Chen et al, 2003). However, it is noted that the specification shows no animal model correlation to data that the polypeptide in the form of a composition (vaccine, pharmaceutical or

medicament) can function in that capacity. Again, the Chen et al, 2003 reference has not been provided. Further, any data regarding the enablement of the claimed invention should be provided in the form of a declaration.

Applicant's arguments filed December 12, 2003 have been fully considered but they are not persuasive. With regard to Carlson et al, 1990 the reference uses mouse mAb to PfHRP1/KP/KAHRP, histidine rich protein 1, knob protein/knob associated histidine rich protein, which is not the same as the protein claimed by Applicant. With regard to Chen et al, this is only a manuscript that appears to have been submitted to a scientific journal (PNAS). It is not clear that this manuscript has ever been reviewed by PNAS, accepted by PNAS or published by PNAS. As stated previously, the specification shows no animal model correlation to data that the polypeptide in the form of a composition (vaccine, pharmaceutical or medicament) can function in that capacity. Any data regarding the enablement of the claimed invention should be provided in the form of a declaration.

The specification, while being enabling for a polypeptide which binds to heparin sulfate or heparin sulfate-like molecules and a method for determining the rosette binding region utilizing the polypeptide, does not reasonably provide enablement for a pharmaceutical, vaccine, medicament or comprising the polypeptide or any amino-terminal part of the polypeptide of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with, which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a pharmaceutical composition, a medicament, vaccine or a composition. The specification teaches the identification of a polypeptide termed PfEMPI, which is useful as a receptor for malaria

erythrocyte membrane protein. The specification fails to teach how the polypeptide or fragment of the polypeptide was used in a pharmaceutical, vaccine or medicament. There are no animal models to show that the polypeptide indeed prevented or treated infection in patients. The development of vaccines and treatment therapies for individuals infected with malaria has been hampered by the fact that there is still no vaccine to prevent malaria. Baruch et al point out (WO 96/33736) that antibodies raised against a particular parasite will only react by parasitized erythrocyte (PE) agglutination with PE from the same strain (page 3). Studies have also shown that the malaria parasite exhibits variant surface antigens in different geographical locations hampering effective development of vaccine and treat therapies. Without clear evidence showing the utility of polypeptides from malaria erythrocyte membrane proteins to protect against malaria, one of skill in the art would not readily know how to use the polypeptides for prevention without undue experimentation. Therefore in view of all of the above and in view of the state of the art, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claimed subject matter.

5. The rejection of claims 39-51 under 35 U.S.C. § 112, first paragraph, because the specification is not enabled for the scope of enablement of a polypeptide comprising any part of SEQ ID NO: 1 is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 13-15, 17, 21, 24 and 33-38 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed April 1, 2003, have been fully considered but

they are not deemed to be persuasive. It is noted that Applicants have not responded to this rejection.

Applicant's arguments filed December 12, 2003 have been fully considered but they are not persuasive. Applicants have asserted that the claimed invention is not directed any part of SEQ ID NO: 1, but rather, the claimed invention is directed to an isolated polypeptide originating from a malaria erythrocyte membrane protein of SEQ ID NO: 1. SEQ ID NO: 1 is the sequence of the complete malaria erythrocyte membrane protein, pfEMP1. The isolated polypeptide consists of an amino-terminal part of SEQ ID NO: 1. Applicants also assert that the claims recite that the amino-terminal part of the sequence comprises domain DBL-1, and thus the claimed invention is not directed to just any portion of SEQ ID NO: 1. However, it is noted that the claims do not set forth how much of SEQ ID NO: 1 is required to constitute an amino-terminal part. The claims recite that the sequence "comprises". Does Applicant intend that the polypeptide only consist of that portion of SEQ ID NO: 1 that is the domain DBL-1? What part of SEQ ID NO: 1 is encompassed in the amino-terminal part?

The specification, while being enabling for a polypeptide which binds to heparin sulfate or heparin sulfate-like molecules and a method for determining the rosette binding region utilizing the polypeptide, does not reasonably provide enablement for a polypeptide comprising any part of SEQ ID NO: 1. The claims are drawn to a polypeptide comprising an amino terminal part of SEQ ID NO: 1 or various amino acids of SEQ ID NO: 1, a vaccine, a pharmaceutical or a medicament comprising a part of SEQ ID NO: 1. The specification lacks guidance to show which part of the amino terminus of SEQ ID NO: 1 would have the claimed activity or which 400, 500 or so amino acids would have the claimed

activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- an amino acid sequence for the claimed protein',
- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity claimed and
- the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen. Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). Therefore, in view of all of the above, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claimed subject matter.

6. The rejection of claims 39-51 under 35 U.S.C. § 102(b) as anticipated by Helmby et al, 1993 (Infection and Immunity, 61/1284-288) is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 13-15, 24 and 33-38 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed April 1, 2003 have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that the prior art discloses proteins termed rosettings, but that proteins are not involved in resetting referring to Fernandez et al, 1999. However, this limitation is not set forth in the claims. Applicants have asserted that the polypeptides have a molecular size of less than 200 kD and that this is a size quite distinct from the known PfEMP1 antigens. However, the molecular weight of the polypeptide is not recited in the claims. Further, the claims recite that the polypeptide comprises an amino-terminal part of the sequence according to SEQ ID NO: 1; the limits of the amino-terminal part of the sequence according to SEQ ID NO: 1 have not been defined. Therefore, Helmby et al would appear to disclose the claimed invention.

Applicants' arguments filed December 12, 2003 have been fully considered but they are not deemed to be persuasive. Applicants have asserted that polypeptides disclosed by HELMBY et al. fail to anticipate or render obvious the claimed invention. Indeed, polypeptides as described HELMBY et al. are distinct from DBL-1. HELMBY et al disclose the isolation of small proteins, termed rosettins. Their surface antigens *P. falciparum* infected red blood cells. However, these rosettins (now know as rifins) are not actually involved in resetting. This is

clearly demonstrated by Feranadez et al. Exp. Med. 1999). In fact, these polypeptides have a molecular weight of 22 or 28 kDa. This stands in distinct contrast to the DBL-I peptide of the claimed invention, which has molecular weight of 48 kDA.

However, it is noted that the each and every claim does not set forth a specific molecular weight. Further, the claims do not set forth how the molecular weight was determined and the claims recite that the polypeptide "comprises" therefore it is not clear what the polypeptide contains. With regard to the molecular weight, since the method of molecular weight determination has not been set fort, it would appear that the prior art discloses the same polypeptide. Similar molecular weights are disclosed in the prior art. Further, the claims recite that the polypeptide comprises an amino-terminal part of the sequence according to SEQ ID NO: 1; the limits of the amino-terminal part of the sequence according to SEQ ID NO: 1 have not been defined. Therefore, Helmby et al would appear to disclose the claimed invention.

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
May 6, 2004